Ref. 10

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 991 407 B9

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**
Note: Bibliography reflects the latest situation

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see page(s) 2

(48) Corrigendum issued on:
13.11.2002 Bulletin 2002/46

(45) Date of publication and mention of the grant of the patent:
28.11.2001 Bulletin 2001/48

(21) Application number: **98919099.6**

(22) Date of filing: **13.03.1998**

(51) Int Cl.[7]: **A61K 31/44**, A61K 9/16, A61K 47/18

(86) International application number:
PCT/EP98/01478

(87) International publication number:
WO 98/040069 (17.09.1998 Gazette 1998/37)

(54) **STABILIZATION OF ACID SENSITIVE BENZIMIDAZOLS WITH AMINO/CYCLODEXTRIN COMBINATIONS**

STABILISIERUNG VON SÄUREEMPFINDLUCHEN BENZIMIDAZOLEN UNTER VERWENDUNG VON AMINOSÄURE/CYCLODEXTRIN KOMBINATIONEN

STABILISATION DE BENZIMIDAZOLES SENSIBLES AUX ACIDES AVEC DES COMBINAISONS AMINO-CYCLODEXTRINE

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
SI

(30) Priority: **13.03.1997 EP 97104200**

(43) Date of publication of application:
12.04.2000 Bulletin 2000/15

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- **DATABASE WPI Week 9332 Derwent Publications Ltd., London, GB; AN 93-255964 [32] XP002079804 & KR 9 208 161 B (HANMI PHARM. IND. CO.,KR) 24 September 1992**

EP 0 991 407 B9

Printed by Jouve, 75001 PARIS (FR)

ingredient by forming a benzimidazole/cyclodextrin inclusion complex.

[0013] It has now been found, that benzimidazoles such as omeprazole can be stabilized by complexation with a cyclodextrin such as β-cyclodextrin in the presence of an amino acid. It has further been found that in this case surprisingly no additional inert or enteric layer is needed to protect particles or a core containing the benzimidazole/cyclodextrin complex and an amino acid. Merely optionally the core may be coated directly with an enteric coating layer.

[0014] Thus, the problem underlying the invention is solved by a pharmaceutical formulation comprising or consisting of

- a benzimidazole derivative as active ingredient, and as excipients
- at least one β-cyclodextrin and/or γ-cyclodextrin and
- at least one amino acid,

wherein the benzimidazole derivative, the at least one cyclodextrin and the at least one amino acid are contained in a cote coated directly with an enteric coating layer,

[0015] The present invention does provide a new pharmaceutical benzimidazole formulation with improved stability features and simplified preparation process.

[0016] The benzimidazole derivative can be a compound which is decomposed in the presence of humidity and especially at a pH ≤ 11, especially ≤ 7. Examples for these benzimidazole derivatives are omeprazole, lansoprazole, leminoprazole, rabeprazole, and pantoprazole. Omeprazole is preferred.

[0017] Further, a specific embodiment of the invention concerns a pharmaceutical formulation, wherein the inclusion complex forming agent is β-cyclodextrin.

[0018] The amino acid useful for the pharmaceutical formulation according to the invention can be an alkaline amino acid, preferably arginine, lysine or hydroxy lysine and especially L-arginine, L-lysine or L-hydroxy lysine; an alkaline dipeptide or a pharmaceutically acceptable alkaline amino acid derivate.

[0019] Further, a specific embodiment of the invention concerns a pharmaceutical formulation, wherein the molar ratio of omeprazole to cyclodextrin is 1 to 10 and preferably 1 to 2.

[0020] Further, a specific embodiment of the invention concerns a pharmaceutical formulation, wherein the molar ratio of the amino acid (preferably L-arginine) to omeprazole is 0.5 to 10 and preferably 1 to 1.

[0021] Further, a specific embodiment of the invention concerns a pharmaceutical formulation, wherein the formulation is a powdered, pelletized or granulated form, optionally processed to tablets.

[0022] The powder, the granulate or the pelletized formulation can be contained in capsules.

[0023] Further, the particles of the powder, of the granulate or of the pelletized formulation can be contained in capsules which are not provided with an enteric coating.

[0024] As examples for enteric coating materials polymeres such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, copolymerized methacrylic acid/methacrylic acid methyl esters or water-based polymer dispersions, for instance, compounds known under the trade name Eudragit® L (Röhm Pharma), or similar compounds can be used. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as dibutylphthalate, diethylsebacat or triethylcitrat. Dispersants such as talc, colorants and pigments may also be included to the enteric coating layer.

[0025] The problem underlying the invention is, in addition, solved by a process for the production of a pharmaceutical composition according to the invention, wherein

(i) a benzimidazole derivative, at least one cyclodextrin, and at least one amino acid are wetted with water and mixed;
(ii) the resulting mixture is dried.

[0026] Further, the problem underlying the invention is solved by a process for the production of a pharmaceutical composition according to the invention, wherein

(i) a benzimidazole derivative, at least one cyclodextrin, and at least one amino acid are wetted with water and mixed;
(ii) the resulting mixture is dried.

[0027] Further, the problem underlying the invention is solved by a process for the production of a pharmaceutical composition according to the invention, wherein

(i) a benzimidazole derivative, at least one cyclodextrin, and at least one amino acid are wetted with water and mixed;

Comparative Example

[0037] Inclusion complexes of omeprazole and β-cyclodextrin were prepared by the same method as described before but without using an amino acid.

[0038] As reference omeprazole and lactose mixtures were prepared, with similar weight-ratios. The molar ratio of omeprazole to β-cyclodextrin and to lactose was 1:2. The result is illustrated in Table II.

Table II: Composition and discoloration of powder mixtures stored at 40 °C at 76% R.H. for 20 days

samples	omeprazole	β-CD	lactose	cellulose acetate phthalate	stored in closed container	stored in open container	O.D. after dissolving the powders
G	+		+		+		0,2
H	+		+	+	+		0,4
I	+	+			+		0,2
J	+	+		+	+		0,4
K	+		+			+	0,8
L	+		+	+		+	2,4
M	+	+				+	0,7
N	+	–		+		+	2,0

[0039] Stability of the inclusion complex in absence of an amino acid seems to be acceptable only by storage in closed containers even in the absence of cellulose acetate phthalate. The pre-sence of cellulose acetate phthalate in all cases enhances the degradation of omeprazole. Comparing the samples stored in closed and in open containers the role of the humidity is quite obvious: the discoloration of omeprazole in open containers is much higher in all cases than in the closed containers. The degradation is significantly accelerated by humidity (samples stored in open containers) and by the presence of cellulose acetate phthalate (acidic additive), the β-cyclodextrin itself is not a significantly better stabilizer than the lactose.

Example 2

[0040] In further experiments the β-cyclodextrin has been suspended in diluted aqueous ammonium hydroxide solution, before omeprazole and arginine has been added. The samples were prepared as described before and stored at 50 °C and 76% R.H. for 7 days. Cellulose acetate phthalate (CAP) (5%w/w) was mixed to all samples after the β-cyclodextrin/omeprazole/arginine amino acid suspensions were dried and powdered. The composition of the samples as well as their discoloration are shown in Table III.

Determination of omeprazole content of samples

[0047] As it is shown in Table IV., the samples showed a good storage stability. The decrease of the omeprazole content in the samples - stored under stressed conditions - does not exceed an absolute value of 0.5%, at samples - stored at ambient temperature - practically no change in active ingredient content was observed.

[0048] Visual observation of the samples showed no color change, except of the sample stored in open container at daylight (see Table IV.). The moisture absorption of the samples - stored at 76% RH. - was remarkable, without significant discoloration (Table V.)

Table IV.: Omeprazole content of the samples after two weeks storage under stressed conditions and 6 months storage at ambient temperature

storage conditions	storage period	omeprazole content (%*±SD) "a"	"b"	Appearance
-	-	12.3±0.08	12.0±0.10	off white powder
40°C, 76% RH	2 weeks	12.0±0.06	11.7±0.05	not changed
ambient temperature - closed container	6 months	12.3±0.23	12.1±0.23	not changed
- open container	6 months		11.3±0.5	very light yellowish color

* related to the dry substance

Table V.: Moisture absorption of the samples

storage conditions	storage period	loss on drying (%) "a"	"b"
-	-	2.79	2.16
40°C, 76% R.H.	2 weeks	9.17	8.23
ambient temperature - closed container	6 months	2.65	2.37
- open container	6 months	-	4.35

Example 4

[0049] 0.64 g omeprazole and 5.08 g β-cyclodextrin (water content: 12%) are homogenized in a mortar, then a solution of 0.33 g lysine in 1.5 ml of 2.5% NH_3 is added and homogenization is continued. Finally the obtained suspension is granulated through a laboratory sieve with 0.4 mm and dried at 45°C for 24 hours. 5.5 g of granules is obtained. omeprazole content: 10.9%

Example 7

[0054] First three mixtures were prepared:

1) 4.1 g omeprazole and 6 g β-cyclodextrin (water content: 11,9 %)
2) 25 g β-cyclodextrin and 55 g water
3) 21 g water and 2,1 g L-arginine

[0055] Then the three mixtures were mixed together and the resulting suspension was spray-dried under the following conditions:

inlet temperature	120 - 125°C
outlet temperature	75 - 80°C
air pressure	2.5 kg/cm^2
feeding speed	4 ml/min

[0056] 37.5 g off-white powder is obtained.

omeprazole content	12.6%
L-arginine content	6.22%
water content (KFT)	5.40%

Example 8

[0057] 509 g pharmaceutical formulation (omeprazole: β-cyclodextrin: arginine) (1:2:1), 163 g microcrystalline cellulose and 55 g hydroxypropylcellulose are mixed for 5 minutes. Then 270 g isopropanol are given to the mixture and mixed for 10 minutes on high level. After that the mixture is extruded and instantly worked up to pellets. The pellets are dried for about 16 - 18 hours at 40 °C.

[0058] The pellets can be filled into hard gelantine capsules optionally enteric coated. Or the pellets are enteric coated with Eudragit L, for example L 100-55, L100 or L 30D according to standard methods.

Claims

1. A pharmaceutical formulation comprising or consisting of

   - a benzimidazole derivative as active ingredient, and as excipients
   - β-cyclodextrin and/or γ-cyclodextrin and
   - at least one amino acid

   wherein the benzimidazole derivative, the at least one cyclodextrin and the at least one amino acid are contained in a core coated directly with an enteric coating layer.

2. Pharmaceutical formulation according to claim 1, in which the benzimidazole derivative is selected from benzimidazole derivatives which are decomposed in the presence of humidity and especially at a pH ≤ 11, especially ≤ 7.

3. Pharmaceutical formulation according to any of the preceding claims, in which the benzimidazole derivative is omeprazole.

4. Pharmaceutical formulation according to any of the preceding claims, in which the cyclodextrin is β-cyclodextrin.

5. Pharmaceutical formulation according to any of the preceding claims, in which the amino acid is a basic amino acid, an alkaline dipeptide or a pharmaceutically acceptable alkaline amino acid derivative, preferably arginine, lysine or hydroxy lysine, especially L-arginine, L-lysine or L-hydroxy lysine; an alkaline dipeptide or a pharmaceutically acceptable alkaline amino acid derivative.

dere ≤ 7.

3. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, bei dem das Benzimidazol-Derivat Omeprazol ist.

4. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, bei dem das Cyclodextrin β-Cyclodextrin ist.

5. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, bei dem die Aminosäure eine basische Aminosäure, ein alkalisches Dipeptid oder ein pharmazeutisch verträgliches alkalisches Aminosäure-Derivat ist, vorzugsweise Arginin, Lysin oder Hydroxylysin, insbesondere L-Arginin, L-Lysin oder L-Hydroxylysin; ein alkalisches Dipeptid oder ein pharmazeutisch verträgliches alkalisches Aminosäure-Derivat .

6. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, **gekennzeichnet durch** ein Molverhältnis von Omeprazol zu Cyclodextrin von 1 bis 10 und insbesondere 1 bis 2.

7. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche, **gekennzeichnet durch** ein Molverhältnis von Aminosäure (vorzugsweise L-Arginin) zu Omeprazol von 0,5 bis 10 und vorzugsweise 1 bis 1.

8. Pharmazeutische Zubereitung nach einem der vorhergehenden Ansprüche in pulveriger, granulierter oder pelletisierter Form, jeweils gegebenenfalls zu Tabletten verarbeitet.

9. Pharmazeutische Zubereitung nach Anspruch 8, **dadurch gekennzeichnet, daß** Pulver, Granulat oder pelletisierte Zubereitung in einer Kapsel enthalten ist.

10. Pharmazeutische Zubereitung nach Anspruch 8, **dadurch gekennzeichnet, daß** die Partikel des Pulvers, des Granulats oder der pelletisierten Zubereitung in einer Kapsel enthalten sind, die nicht mit einem enteralen Überzug versehen sind.

11. Verfahren zur Herstellung einer pharmazeutischen Zubereitung nach einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet, daß** man

    (i) ein Benzimidazol-Derivat, mindestens ein Cyclodextrin und mindestens eine Aminosäure mit Wasser befeuchtet und mischt;

    (ii) die resultierende Mischung trocknet.

12. Verfahren zur Herstellung einer pharmazeutischen Zubereitung nach einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet, daß** man

    (i) ein Benzimidazol-Derivat, mindestens ein Cyclodextrin undmindestens eine Aminosäure mit Wasser befeuchtet und mischt;

    (ii) die resultierende Mischung trocknet; und

    (iii) die Verfärbung der Zubereitung untersucht und sofern ein verfärbtes Produkt erhalten wird, das verfärbte Produkt verwirft, eine andere Aminosäure wählt und die Stufen (i) bis (iii) wiederholt, bis ein unverfärbtes Produkt erhalten wird.

13. Verfahren nach Anspruch 11 oder 12, **dadurch gekennzeichnet, daß** man bei Stufe (i) gemäß Anspruch 11 das Mischen durch Feuchtkneten durchführt.

14. Verfahren nach einem der Ansprüche 11 bis 13, **dadurch gekennzeichnet, daß** man bei Stufe (i) gemäß Anspruch 11 ammoniakalisches Wasser oder Wasser frei von Ammoniak als Wasser verwendet.

15. Verfahren nach einem der Ansprüche 11 bis 14, **dadurch gekennzeichnet, daß** man bei Stufe (ii) gemäß Anspruch 11 das Trocknen durch Gefriertrocknen, Sprühtrocknen oder Vakuumtrocknen durchführt.

13. Procédé selon la revendication 11 ou 12, **caractérisé en ce que**, au cours de l'étape (i) de la revendication 11, le mélange s'effectue par pétrissage par voie humide.

14. Procédé selon l'une quelconque des revendications 11 à 13, **caractérisé en ce que**, au cours de l'étape (i) de la revendication 11, l'eau est de l'eau ammoniacale ou ne comporte pas d'ammoniac.

15. Procédé selon l'une quelconque des revendications 11 à 14, **caractérisé en ce que**, au cours de l'étape (ii) de la revendication 11, le séchage s'effectue par lyophilisation, séchage par pulvérisation ou dessiccation sous vide.